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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	SINGER *et al.*
Serial No.	:	10/773,535
Filed	:	February 5, 2004
For	:	METHOD OF STABILIZING LANSOPRAZOLE
Examiner	:	Patricia L. Morris
Art Unit	:	1625

Mail Stop Amendment
Commissioner for Patents
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Declaration Under 37 C.F.R. § 1.132

I, CLAUDE SINGER, Ph.D., of 8/8 David Elazar, Kfar Saba 44358, Israel, declare as follows:

I. BACKGROUND

1. I am a named co-inventor of U.S. application Serial No. 10/773,535 ("the '535 application") filed February 5, 2004.

2. I received my Ph.D. degree in 1985 from The Polythehnic Institute Bucharest, Rumania. Since 1986, I have worked for Teva Pharmaceutical Industries, Ltd. ("Teva"). I am currently Teva's API Global R&D Management. In that position, I am responsible for Global R&D Project Coordination.

3. I have reviewed and understood the specification and claims of U.S. patent application Serial No. 10/773,535 entitled "Method of Stabilizing Lansoprazole".

4. I am familiar with the prosecution of the '535 application and have reviewed and understood the Office Action mailed July 18, 2006 ("the Office Action"). The Office Action alleges that lansoprazole as disclosed in various patents, including U.S. Pat. No. 6,002,011 ("*Kato et al.*"), anticipate claims 33-38, and 42-45 of the present application.

5. I have reviewed and understood U.S. Patent No. 6,002,011 issued on December 14, 1999, to Kato *et al.*, ("the '011 patent").

II. PREPARATION OF LANSOPRAZOLE ACCORDING TO THE '011 PATENT

6. I have directly supervised the repetition of the preparations of lansoprazole according to Reference Example 6, Example 1 and Comparative Example 1 of the '011 patent. These repetitions of preparing lansoprazole are as follows.

7. The repetition of Reference Example 6 was carried out as follows. To Vanadium (IV) acetylacetonate in ethanol was added the starting material sulfide, TFPB (2-[[3-methyl-4-(2,2,2-trifluorethoxy)-2-pyridinil]thio]-1H benzimidazole) to obtain a solution; at room temperature (RT) 30% H_2O_2 was added dropwise to the solution over a period of 10 minutes and subsequently stirred at RT for 5 hours; aqueous sodium thiosulfate was added to the mixture at RT while vigorously stirring for 10 min.; the obtained slurry was filtered under reduced pressure and washed with ice-cold ethanol/H_2O (8:2); to the resulting crystals ethanol/H_2O (9:1) was added and the suspension was heated to 65°C; the suspension was then filtered hot under reduced pressure; the clear filtrate was ice-cooled for 1 hour; the resulting solid was filtered under reduced pressure and washed with ice-cold ethanol/H_2O (8:2), then dried in a vacuum oven at RT overnight. The obtained material was given the identifier KC-P-053.

8. The material obtained according to Reference Example 6, identified as KC-P-053, was subsequently used in the preparation of Example 1 and Comparative Example 1 as in the '011 patent.

9. The repetition of Example 1 was carried out as follows. To 58 ml of ethanol-water mixture(9:1) was added 54μl of 25% aqueous ammonia solution. While the solution was heated to about 60°C, 10g. of KC-P-053, was added to the solution to be dissolved. The insolubles were removed by filtration off while the solution was hot. The filtrate was cooled with ice to precipitate crystals. The precipitated crystals were collected by filtration to give wet crystals of 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methylsulfinyl] benzimidazole. Thus obtained wet crystals were suspended in 41ml of water and the suspension was stirred for 1 hour while keeping the temperature at 30°C. The emerged crystals were recovered by filtration, washed with 10 ml of water, and then were dried at 40°C in vacuum for 10 hours to give 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methylsulfinyl]benzimidazole as white crystalline powder, which was given the identifier KC-P-054.

10. The repetition of Comparative Example 1 was carried out as follows. To 58 ml of ethanol-water mixture(9:1) was added 54 μl of 25% aqueous ammonia solution. The mixture was heated to about 60°C, followed by addition of 10.0 g. of KC-P-053, which was dissolved. Insolubles were removed off by filtration while the mixture was hot. The filtrate was cooled with ice to precipitate crystals. The precipitated crystals were collected by filtration to give 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methylsulfinyl]-benzimidazole as wet crystals. The crystals were dried at 40°C for 10 hours in vacuum to give 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methylsulfinyl]-benzimidazole as white crystalline powder, which was given the identifier KC-P-055.

III. ANALYSIS OF LANSOPRAZOLE ACCORDING TO THE '011 PATENT

11. Samples of KC-P-054 and KC-P-055 were stored under different conditions for a period of 3 months as shown in Table 1. The impurity profile was determined using the HPLC USP method analysis.

Table 1: Impurity Profile of Lansoprazole Prepared According to the '011 patent.

Sample	Months	Conditions	Color Visual	Impurity profile in percent (w/w)				
				LNP-NO	LNP-SO_2	TFPB	Other	Total
KC-P-054	0		white	0.04	0.14	0.04	0.02	0.24
	3	2-8°C	white	0.03	0.14	0.03	0.02	0.22
	3	25°C/60%RH	creamy	0.03	0.14	0.03	0.02	0.22
	3	40°C/75%RH	brownish	0.03	0.14	0.14	0.06	0.55
KC-P-055	0		white	0.04	0.16	<0.02	0.02	0.22
	3	2-8°C	white	0.04	0.17	<0.02	0.02	0.23
	3	25°C/60%RH	creamy	0.04	0.17	0.06	0.03	0.31
	3	40°C/75%RH	brownish	0.04	0.17	0.34	0.11	0.99

In the above table LNP-NO, LNP-SO_2, and TFPB represent the most common impurities of Lansoprazole, LNP-SO_2 being the sulfone impurity and TFPB the sulfide impurity. Further, the amount of water in the lansoprazole samples KC-P-054 and KC-P-055 was determined to be 0.15% and 0.44% respectively.

12. It is my opinion, that each of the Lansoprazole samples KC-P-054 and KC-P-055, prepared according to Example 1 and Comparative Example 1 in the '011 patent, lack in purity and stability compared to the stable Lansoprazole in Examples 2 and 3 in the specification of the '535 application upon storage. When stored for three months at 40°C and 75% Relative Humidity KC-P-054 and KC-P-055 were discolored (appearing brownish) and included increased amounts of impurities, in particular the sulfide impurity. In contrast, the stable Lansoprazole of the '535 showed no discoloration (remaining white) and included less than 0.1% (w/w) of each of the sulfone (0.02%) and the sulfide (0.03%) impurities.

13. Thus, in my opinion, lansoprazole of the '535 application is stable upon storage whereas the lansoprazole prepared according to the prior art '011 patent is less stable.

14. I declare that all statements made herein are true, and that all statements made herein on information and belief are believed to be true, and that all statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code, and that any willful false statement may jeopardize the validity of any United States Patent that would issued from the '535 application.

Dated: 03.07.08 Signed: _____

Claude Singer, Ph.D.